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Synthesis and pharmacological evaluation of 1-[2,6,8-trisubstituted -4(3H)-oxoquinazolin-3-yl]-3-(4-substituted phenyl) thiobarbiturates+

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Twelve new 1-[2, 6, 8-trisubstituted-4(3H)-oxoquinazolin-3-yl]-3-(4-substituted phenyl) thiobarbiturates (17-28) were synthesized by reacting 2, 6,8-trisubstituted-3-[N³-(4-substituted phenyl) thioureido]-4(3H)-quinazolones (5-16) with malonic acid in presence of acetyl chloride.These thioureidoquinazolone intermediates were obtained, on the other hand, by the condensation of 3-amino-2,6, 8-trisubstituted-4(3H)-quinazolones (1-4) with different 4-substituted phenyl isothiocyanates. All these compounds were characterized by analytical and spectral data. Compounds 27, 24 and 20 were found to possess good sedative properties while compounds 18, 26 and 28 exhibited significant anticonvulsant activity.

Quinazolones are known to be biologically versatile compounds possessing several pharmacological properties[1,2], including sedative-hypnotic[3] and anticonvulsant[4]. The extent of the pharmacological effect of quinazolone derivative depends on the active group with which it is attached[5]. Recently, the synthesis and antimicrobial activities of N-(substituted-3, 4-dihydro-4-oxoquinazolin-3-yl) acetoacetamides and their β-(4-substituted phenyl) azo analogs were reported from our laboratory[6]. Certain thiobarbiturate derivatives, on the other hand, are also well known to be associated with significant CNS depressant properties[7]. Encouraged by these findings, some new 1-[2, 6,8-trisubstituted-4(3H)-oxoquinazolin-3-yl] - 3 - (4-substituted phenyl) thiobarbiturates, containing both 4(3H)-quinazolone and thiobarbiturate systems interconnected, were synthesized, with a view to generate compounds with interesting CNS activity.

The reaction sequence leading to the formation of the title compounds was outlined in Scheme-1. The key intermediates 2,6,8-trisubstituted-3 - [N³-(4-substituted phenyl) thioureido]-4(3H)-quinazolones (5-16) were obtained by reacting respective 3-amino-2, 6, 8-trisubstituted-4 (3H)-quinazolones (1-4)[8,9] with different 4-substituted phenyl isothiocyanates[10-12] in ethanol. For instance, condensation of 3-amino-6,8-dibromo-2-methyl-4(3H)-quinazolone (1) with phenyl isothiocyanate in ethanol resulted a colourless solid which was purified by recrystallization from chloroform-ethyl acetate (1:2) mixture and characterized as 6,8-dibromo-2-methyl-3-(n³-phenyl thioureido)-4(3H)-quinazolone (7) on the basis of its elemental analysis and spectral data. Its IR (KBr) spectrum showed characteristic absorptions in cm^{-1} at 3320 (NH str), 1665 (CO-N), 1630 (C=N), 1590 (NH bend) and 1170 (C=S). PMR(DMSO-d_6) spectrum exhibited proton signals for presence of Ar-CH_3, 2xNH and aromatic-H groups including quinazolones 5-H, respectively (Table-1) while its mass spectrum showed molecular ion peak at m/z 466 (41%).

These thioureido quinazolone intermediates (5-16) were cyclized with malonic acid in presence of acetyl chloride to afford pale yellow solids. They were purifed and characterized by analytical and spectral data as 1-[2, 6, 8-trisubstituted-4(3H)-oxoquinazolin-3-yl]-3-(4-substi-

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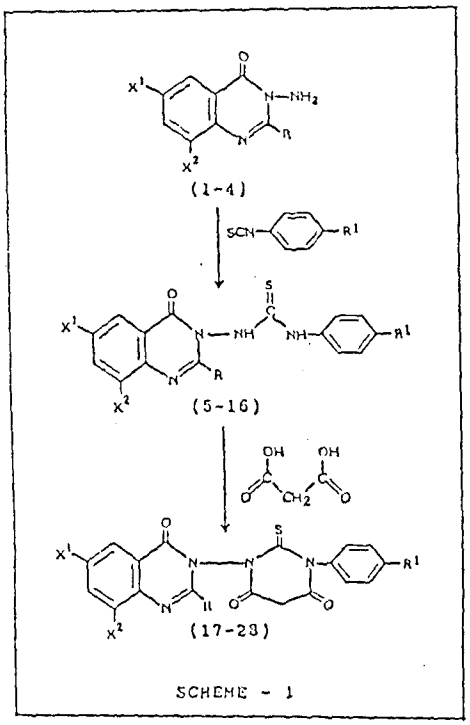

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tuted phenyl) thiobarbiturates (17-28). For example, 6, 8-dibromo-2-methyl-3-(N^3-phenyl thioureido)-4(3H)-quinazolones (7) on cyclization reaction with malonic acid in presence of acetyl chloride gave pale yellow solid which was purified by recrystallization from chloroform-ethanol (1:5) mixture and characterized as 1-[6,8-dibromo-2-methyl-4(3H)-oxoquinazolin-3-yl]-3-phenyl thiobarbiturate (19). Its IR (KBr) spectrum showed peaks in cm^{-1} at 3460 (CH_2), 1685 (CO-N), 1655 (C=O), 1625 (C=N) and 1180 (C=S). Its PMR (DMSO-d_6) spectrum displayed characteristic proton signals for Ar-CH_3, CO-CH_2-CO and aromatic-H groups including quinazolone's 5-H, respectively (Table-2) and mass spectrum showed strong molecular ion peak at m/z 534 (26%). The mass spectral fragmentation and satisfactory elemental analysis of the compound further confirmed the structure assigned.

All the compounds synthesized were investigated for sedative and anticonvulsant activities using standard techniques such as pentobarbitone-induced narcosis[13,14] and pentylenetetrazole-induced convulsions[14,15] in mice.

EXPERIMENTAL

Melting points were determined in open capillaries on electrically heated block and are uncorrected. Purity of the compounds was checked by TLC using silica gel G. IR (KBr) spectra were recorded on Perkin-Elmer model-1600 spectrometer, PMR spectra on Perkin-Elmer EM-390-90 MHz spectrometer, using TMS as internal reference and mass spectra on Jeol JMS-D 300 double beam spectrometer.

3-Amino-2,6,8-trisubstituted-4(3H)-quinazolones (1-4)[8,9] and different 4-substituted phenyl isothiocyanates[10-12] were prepared by reported methods.

Synthesis of 2,6,8-trisubstituted-3-[N^3-(4-substituted phenyl) thioureido]-4(3H)-quinazolones (5-16)-A General Procedure :

An equimolar (0.01 mol) mixture of appropriate 3-amino-2,6,8-trisubstituted-4(3H)-quinazolone and corresponding 4-substituted phenyl isothiocyanate was refluxed in dry ethanol (40 ml) for 8 h on water bath. The reaction mixture was poured onto crushed ice and the resultant solid was washed with cold water and purified by recrystallization from chloroform-ethyl acetate (1:2) mixture. Physical and analytical data of these compounds were given in Table-1.

Synthesis of 1-[2, 6, 8-trisubstituted-4(3H)-oxoquinazolin-3-yl]-3-(4-substituted phenyl) thiobarbiturates (17-28)-A General Procedure :

A mixture of appropriate 2,6,8-trisubstituted-3-[N^3-(4-substituted phenyl) thioureido]-4(3H)-quinazolone (0.01 mol) and malonic acid (0.02 mol) in acetyl chloride (10 ml) was refluxed for 3 h. on water bath. The solution was poured onto crushed ice while stirring. The resulting solid was filtered off, washed with cold water and purified by recrystallization from chloroform-ethanol (1:5) mixture. Similarly, twelve compounds were synthesized and physical and analytical data of these compounds were presented in Table-2.

Pharmacological evaluation

Toxicity and gross behavioural studies of the test compounds as suspension in 0.5% w/v carboxymethylcellulose were carried out by standard methods[15,17] in oral dose of 50 to 1500 mg/kg in albino mice. Sedative activity by pentobarbitone-induced narcosis[13,14] and anti-

Table 1 - Physical and analytical data of compounds 5-16

Compd*	Substituents			Mol. Formula	M.P °C	Nitrogen analysis (%) obs. (Calc.)	Yield %
	X^1&X^2	R	R^1				
5	Br	methyl	Br	$C_{16}H_{11}ON_4SBr_3$	160	10.15(10.24)	72
6	Br	methyl	Cl	$C_{16}H_{11}ON_4SBr_2Cl$	180	11.09(11.15)	73
7	Br	methyl	H	$C_{16}H_{12}ON_4SBr_2$	172	11.90(11.97)	69
8	Br	phenyl	Br	$C_{21}H_{13}ON_4SBr_3$	176	09.13(09.20)	72
9	Br	phenyl	Cl	$C_{21}H_{13}ON_4SBr_2Cl$	238	09.86(09.92)	75
10	Br	phenyl	H	$C_{21}H_{14}ON_4SBr_2$	249	10.51(10.57)	70
11	H	methyl	Br	$C_{16}H_{13}ON_4SBr$	168	11.99(11.94)	70
12	H	methyl	Cl	$C_{16}H_{11}ON_4SCl$	80	16.21(16.26)	69
13	H	methyl	H	$C_{16}H_{14}ON_4S$	162	18.01(18.06)	65
14	H	phenyl	Br	$C_{21}H_{15}ON_4SBr$	164	12.38(12.42)	68
15	H	phenyl	Cl	$C_{21}H_{15}ON_4SCl$	128	13.72 (13.78)	67
16	H	phenyl	H	$C_{21}H_{16}ON_4S$	158	15.00(15.05)	72

*All compounds were recrystallized from chloroform-ethyl acetate (1:2) mixture. Compounds 8-10 were pale yellow in colour while rest of the compounds were colourless. Satisfactory C&H analyses were also obtained. IR (KBr) spectra of all the compounds showed characteristic peaks in cm^{-1} for NH str (3290-3350), CO-N (1660-1690), C=N (1625-1640), NH bend (1585-1605) and C=S (1150-1195). PMR (DMSO-d_6) in δ ppm : Compd. 7:2.45 (s, 3H, Ar-CH_3), 6.9 (br, 2H, 2XNH), 7.2-8.15 (m, 7H, Ar-H including quinazolone's 5-H proton at 8.05), Compd.11:2.32 (s, 3H, Ar-CH_3), 6.72-7.55 (m, 8H, Ar-H including quinazolone's 5-H at 6.80).

convulsant activity against pentylenetetrazole-induced clonic convulsions[14,16] in mice were determined by standard methods at oral dose of 100 mg/kg as 0.5% carboxymethylcellulose suspension of the title compounds, employing diazepam at a dose 10 mg/kg as reference standard under similar conditions and the data of sedative activity of the test compounds were presented in Table-2.

RESULTS AND DISCUSSION

Gross behavioural studies revealed that all the title compounds produce significant CNS depression. Toxicity studies indicate that compounds 24 and 27 were found to be lethal at a dose of 1000 mg/kg wherein 50% mortality was recorded in test animal groups as a result of severe depression followed by considerable loss of righting reflex after 2 h and 6 h of administration, respectively, while the rest of the compounds were non-toxic as no mortality was observed in experimental animals upto a dose of 1500 mg/kg. All the test compounds were found to potentiate the pentobarbitone-induced narcosis in experimental animals. Of them, compounds 27, 24 and 20 were almost on par with the reference drug, diazepam, but of course at ten-fold increased concentration, in their action. Anticonvulsant activity studies indicate that compounds 18, 26 and 28 were comparable with that of the standard, diazepam in their potency but of course, again at ten-fold increased concentration as the experimental animals administered with these three compounds were recovered within 16 to 18 minutes similar to the observation recorded with the standard. The rest of the compounds did not protect the experimental animals from the pentylenetetrazole-induced convulsions. However, they delayed the mortality of animals by more than 4 to 20

Table 2 - Physical and analytical parameters and sedative activity data of compounds 17-28

Compd*	Substituents			Mol. Formula	M.P °C	Nitrogen analysis (%) obs. (Calc.)	Sedation+ %
	X^1&X^2	R	R^1				
17	Br	methyl	Br	$C_{19}H_{11}O_3N_4SBr_3$	102	09.03(09.11)	27
18	Br	methyl	Cl	$C_{19}H_{11}O_3N_4SBr_2Cl$	168	09.86(09.82)	35
19	Br	methyl	H	$C_{19}H_{12}O_3N_4SBr_2$	103	10.38(10.45)	21
20	Br	phenyl	Br	$C_{24}H_{13}O_3N_4SBr_3$	116	08.20(08.27)	56
21	Br	phenyl	Cl	$C_{24}H_{13}O_3N_4SBr_2Cl$	124	08.81(08.85)	33
22	Br	phenyl	H	$C_{24}H_{14}O_3N_4SBr_2$	138	09.30(09.36)	26
23	H	methyl	Br	$C_{19}H_{13}O_3N_4SBr$	129	12.19(12.25)	29
24	H	methyl	Cl	$C_{19}H_{13}O_3N_4SCl$	104	13.50(13.58)	59
25	H	methyl	H	$C_{19}H_{14}O_3N_4S$	132	14.75(14.81)	43
26	H	phenyl	Br	$C_{24}H_{15}O_3N_4SBr$	120	10.72(10.79)	29
27	H	phenyl	Cl	$C_{24}H_{15}O_3N_4SCl$	57	11.85(11.80)	61
28	H	phenyl	H	$C_{24}H_{16}O_3N_4S$	162	12.70(12.73)	19
Diazepam	—	—	—	—	—	—	62

* All compounds were recrystallized from chloroform-ethanol (1:5) mixture. Yields were between 55-75%. Satisfactory C & H analyses were also obtained. IR (KBr) spectra of all the compounds exhibited characteristic peaks in cm^{-1} for CH_2 (3390-3480), CO-N (1670-1700), C=N (1620-1640) and C=S (1165-1220). PMR (DMSO-d_6) in δ ppm.: Compd. 19: 2.53 (s, 3H, Ar-CH_3), 2.70 (s, 2H, CO-CH_2-CO), 6.95-7.62 (m, 7H, Ar-H including quinazolone's 5-H at 7.45); Compd. 21: 2.82 (s, 2H, CO-CH_2-CO), 6.52-7.45 (m, 11H, Ar-H including quinazolones 5-H at 7.34), Compd. 23: 2.10 (s, 3H, Ar-CH_3), 2.65 (br, 2H, CO-CH_2-CO), 7.12-8.35 (m, 8H, Ar-H including quinazolones 5-H at 8.35).
+ Average of triplicate studies on the effect on pentobarbitone-induced narcosis.

minutes as compared to the control group. Many of the title compounds did not exhibit significant sedative and anticonvulsant activities because of the unsubstituted 5th position of the barbiturate group.

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